REMARKS/ARGUMENTS

In response to the Rejection mailed August 25, 2004, Applicants have amended claims 41 and 48, added new claims 58-63 and present the following remarks. Claims 41, 42, 44-50 and 54-63 are pending. Claims 1-40, 43 and 51-53 have been canceled.

The specification was objected to as not indicating the parent patent applications on line 1 of the specification from which priority is claimed. The specification has been amended accordingly.

Claims 41-50 and 54-57 were rejected under 35 USC 112, second paragraph as being indefinite in several recitations. Specifically, the term "derived" in claim 1 is objected to because "derived" may refer to making a chemical derivative. Since claim 1 is canceled, it appears the examiner is referring to Claim 41, which has been amended to substitute different language for comparable meaning.

Claim 41 was considered indefinite by reciting "encoded at least in part". As presently amended, this claim is not indefinite as the minimal "part" is defined by feature (a) of claim 1.

Claim 41 was considered indefinite by reciting "at risk of developing a tumor". Claim 41 has been amended to clarify that the tumor is the B-cell lymphoma and the subject either has or previously had the tumor.

Claim 48 was considered to lack antecedent basis for "the polypeptide". The claim has been amended to avoid this language.

Claims 41-50 and 54-57 were rejected under 35 USC 112, first paragraph, for lack of enablement. The examiner specifically notes that the specification fails to support using any self-antigen for the treatment of a tumor and also fails to support using a B-cell lymphoma immunoglobulins antigen for any tumor. The contention is that undue experimentation is needed to use a B-cell lymphoma vaccine for different types of tumors and that other types of tumor vaccines would be useful against B-cell lymphoma. This rejection is respectfully traversed.

While not agreeing with the reasons for the rejection, applicants have amended the claims without prejudice to recite that the polypeptide self-antigen contains an epitope

from a B-cell lymphoma. Also, the claims now indicate that the polypeptide may be used as a vaccine for B-cell lymphoma patients. Accordingly, this rejection is moot and should be withdrawn.

Applicants take exception to the statement that "Thus, applicants is not enabled for any vaccine composition." While the scientific literature shows many failed attempts at cancer vaccines, several different compositions have showed some positive results. While far from completely effective in all patients, considerable data has shown some improvement with some compositions. For example, effective treatment of melanoma with over 30% remission rates (data from a competitor of the assignee) may not be perfect but it does represent a success. Various types of antigens from B-cell non-Hodgkin's lymphoma have been used with some success (when the patient was not too close to death) as shown in the references of record. The rejection even relies on some of the successful results to use in rejections under 35 USC 102 and 103. Furthermore, attached are publications that provide some of the data from the Phase I clinical trials of 16 patients with B-cell lymphomas and the positive results there from. Therefore, applicants have enabled producing a composition and shown that it is likely to work and subsequently proven that the claimed composition is effective as a vaccine.

The examiner has cited publications indicating that a vaccine for cancer is still in the future and those cancer vaccines are not ready to replace standard therapies. These statements were somewhat reasonable at the time the supporting publications were written because most tumors lack an FDA approved vaccine (and still do today). However, applicants are not suggesting that standard therapies be abandoned but rather that the present invention is an additional treatment, particularly with a particular self-antigen used to treat a B-cell lymphoma. Presently, the claimed method is not FDA approved. It is the subject of clinical trials; some of which are completed and some of the data are in the attached exhibit. The theoretical objects presented in the publications a few years are now moot in view of actual experimental results.

The present claims have been narrowed substantially without prejudice to expedite prosecution of this application only as the example of treating B-cell lymphoma

patients with a B-cell lymphoma specific epitope vaccine is perhaps best exemplified. As such this rejection is moot and should be withdrawn.

Claims 41-44, 46-50 and 54-47 were rejected under 35 USC 112, first paragraph as enabling only treating a B-cell lymphoma with a scFv antigen having the full complement of both VH and VL domains of 3 CDRs each. To support the examiner's speculation as to what is needed, he refers to Benvenuti et al to urge that the "highly specific anti-idiotypic immune response that strictly depends on the quanternary structure of the idiotype". Applicants agree that the three-dimensional structure of the polypeptide antigen is probably important. However, the full set of CDRs may not be the critical feature.

On theoretical grounds, one might conclude that an antigen, which is identical to or most closely resembles the natural tumor antigen, would be best. However, the examples in the specification are a single chain antibody which has only a small part of the natural surface immunoglobulins, a single chain antibody is an unnatural molecule with only one chain rather than the four in the natural surface immunoglobulins and the configuration of domains in a scFv are held in an unnatural position by an artificial linker. With so many differences, it is mere speculation on the examiner's part as to which portions are critical and whether one or more of the CDRs may be omitted.

Furthermore, as noted in the specification and claims, the antigen being use was individually designed for the particular subject's B-cell lymphoma. As suggested by the Benvenuti reference, unrelated B-cell lymphoma antigens are not expected to be reactive. Therefore, even if certain combinations of CDR's are critical, while others are not, for one B-cell lymphoma tumor antigen, there is no indication that the same CDRs are critical or not for another B-cell lymphoma tumor antigen from a different individual.

Applicants had noted that many idiotypic polypeptide vaccines do not induce a good immune response without customizing the linker. As shown in the specification examples, applicants have noted that when the linker is changed the VL and VH are arranged differently and induce a different immune response with many linkers rendering the molecule completely useless as a vaccine. Applicants solved this problem by generating many polypeptides each with different linkers, the subject of which is

mentioned in claims 13-16. Each of the many polypeptides was screened to select the best one.

Benvenuti et al does not even look at the issue of the importance of the linker. They are looking at one small piece of the puzzle from one experiment. Of course it would be preferred to have as much of the surface immunoglobulins as possible to most closely resemble the natural tumor antigen on theoretical grounds alone. However, in both Benvenuti et al and the present invention, we are dealing with scFv mimicking only part of the natural tumor antigen.

While Benvenuti et al suggests that a different immune response is generated from scFv with both VH and VL as compared to only one, this does not indicate how many CDRs and of what type are needed. Also, because each patient's B-cell lymphoma surface immunoglobulins idiotype is different, it is mere speculation to state exactly which CDRs on which chains are essential.

By contrast, the present claims recite that the polypeptide self-antigen is "in correctly folded form, without a need for denaturation and renaturation and mimics said surface immunoglobulin epitope or epitopes in their native form". Benvenuti et al is immunizing the recipient with a naked DNA whereas applicants are immunizing the recipient with a polypeptide self-antigen. It is not clear whether their polypeptide (assuming one is even made in vivo) is correctly folded or not, we only know the immune response to it and therefore, Benvenuti et al does not state what is needed for a protein-based antigen to be effective.

Also, the present claims recite that the polypeptide self-antigen "is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials". Therefore, the present claims only enabled polypeptide self-antigens, regardless of which combination of linkers, chains and CDRs needed. Accordingly, the rejection should be withdrawn.

Claims 41-47 and 54 were rejected under 35 USC 102(b) as being anticipated by Casper et al. The examiner contends that the method for administering the fusion protein vaccine taught is the same as that claimed. This rejection is respectfully traversed.

The polypeptide produced by Casper et al is a fusion protein of the scFv and GM-CSF. Because another protein is fused to it, there is no assurance that the polypeptide is correctly folded or that the specific antigenic epitope is maintained. Indeed, the data shown in Figure 2 indicates that the peptide is an inferior immunogen to the natural antigen conjugated to KLH. The same figure suggests that the DNA encoding the scFv is even superior to the scFv protein fused to GM-CSF. This suggests that the GM-CSF protein portion fused to the scFv is detrimental, the most likely reason being interfering with protein folding or blocking of the epitope. Either way, this suggests that the polypeptide self-antigen in Casper et al is not "in correctly folded form" as recited in claim 41 feature (c).

Furthermore, claim 41 feature (d) indicates the polypeptide "is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials." The vaccine in Casper et al contains GM-CSF, a well-known material for enhancing the immune response. The other polypeptide antigen in Casper et al is conjugated to KLH, a well-known adjuvant. Neither composition, meets the requirements of claim 41 feature (d). As noted above, the scFv containing composition had inferior antigenicity and therefore one would not be motivated to remove GM-CSF for fear of a further lessening of the immune response. Accordingly, Casper et al does not anticipate the presently claimed invention.

Furthermore, newly added claim 58 recites the polypeptide antigen is "not fused or conjugated to another polypeptide." This is clearly different from Caspar et al. Also newly added claims 59 and 60 recite that the polypeptide antigen was produced in 1) plant cells by 2) transient expression, neither feature being described in Caspar et al. Plant cells have a different physiology from animal cells and therefore one may not assume that they will fold and process the polypeptide in the same manner as naturally occurs in human cells. Therefore, these claims are also not suggested by Caspar et al.

Claims 41-47 were rejected under 35 USC 102(b) as being anticipated by Hawkins et al. The examiner contends that Hawkins teaches using an scFv mimicing the surface immunoglobulins of a B-cell lymphoma used as a vaccine. This rejection is respectfully traversed.

As stated above for the rejection over Caspar et al, there is no indication that the polypeptide is folded correctly or that is it capable of inducing an immune response without an adjuvant or immunostimulatory agent. The approach of using DNA vaccines lacks any suggestion of a correctly folded protein being produced because the scFv nucleic acid construct is artificial. Accordingly, the rejection should be withdrawn.

Again, note the comments above regarding the newly added claims.

Claims 41-50 and 54-57 were rejected under 35 USC 103 as being unpatentable over Caspar et al in view of Tang et al and Hsu et al. Caspar et al was applied above. Tang et al is cited to disclose selecting scFvs from genes with randomized linker DNA sequences. Hsu et al is cited to disclose using a type of B-cell lymphoma antigen to treat patients. From these, the examiner concludes it obvious to optimize the scFv linker and to use an appropriate dose to vaccinate against the B-cell lymphoma. This rejection is respectfully traversed.

All of the comments above regarding the deficiencies of Caspar et al apply here as well. None of the secondary references compensate for the basic deficiencies of not teaching a correctly folded polypeptide or a polypeptide that will elicit an immune response without an adjuvant or immunostimulatory material.

Even if one accepted Tang et al as teaching linker randomization for the present polypeptide, the randomization process used in Tang et al is performed differently and would produce a different result from the present invention's linker optimization. Tang et al's linker is 18 amino acids long, being encoded by $(SNN)_{18}$ as stated in the sentence bridging pages 15682 sand 15683. The Tang et al linker is a series of truly random nucleotides. Claims 55-57 provide for "a repeated pattern of degenerate repeated triplet nucleotides" with specific nucleotides at certain locations. This is a controlled set, not a truly random chain. Thus no combination of references suggests these features.

Hsu et al teach fusing the patients B-cell lymphoma to a mouse B-cell lymphoma cell line to make a hybrid cell and to recover full-length immunoglobulins produced by such a hybridoma. These immunoglobulins were conjugated to KLH (as an immunostimulating adjuvant) and used as an antigen along with threonyl-muramyl dipeptide as an immunostimulatory agent. The antigen has natural full-length

immunoglobulins chains, some of which are human and some of which may be mouse. No combination can give a single chain antibody. Furthermore, both adjuvants and immunostimulating materials are added to the Hsu et al vaccine. This is quite different from the present invention, which "is capable of inducing an immune response ... without the need for adjuvant or other immunostimulatory materials".

It should be noted that Caspar et al and Hsu et al publications are both from the same group of scientists and that combined they provide strong motivation to use a variety of different adjuvants and immunostimulatory agents and also a negative teaching to make or use an antigen without such enhancers. Therefore, even if combined, the present invention is not taught and therefore the rejection should be withdrawn.

Claims 41-50 and 54-57 were rejected under 35 USC 103 as being unpatentable over Hawkins et al in view of Tang et al and Hsu et al. Hawkins et al was applied above noting the lacking of teaching a randomized library of linkers and a particular dosage. Tang et al and Hsu et al are cited as above. From these, the examiner concludes it obvious to optimize the scFv linker and to use an appropriate dose to vaccinate against the B-cell lymphoma. This rejection is respectfully traversed.

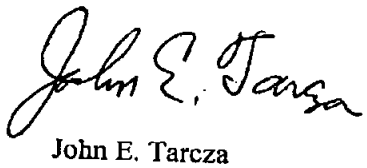
All of the comments above regarding the deficiencies of Hawkins et al, Tang and Hsu et al apply here as well. This rejection is essentially the same as the one above with Hawkins et al being roughly equivalent to Caspar et al. However, as above, Hawkins et al has the same deficiencies as Caspar et al and a few others. Accordingly, for the reasons given above, this rejection should also be withdrawn.

Claims 41-50 and 54-57 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 41-50 of co-pending application 10/067,790 in view of Tang et al. The present claims have been amended and as mentioned above, the linker in Tang et al is of a different type from that claimed. Therefore the rejection should be withdrawn for the reasons given in response to the rejection using Tang above. In any event, applicants request such an issue be readdressed and resolved once the claims are in condition for allowance in either 10/067,790 or the present application.

In view of the above amendments and comments, the claims are now in condition for allowance and applicants request a timely Notice of Allowance be issued in this application. If needed, applicants pctition for sufficient extension of time for consideration of this paper.

The commissioner hereby is authorized to charge payment of any fees, including extension of time fees, under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,



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Attachments: Published Abstract with data from Phase I trials.

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**Abstracts from the American Society of Hematology
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[609] Plant Derived Single-Chain Fv Idiotype Vaccines Are Safe and Immunogenic in Patients with Follicular Lymphoma: Results of a Phase I Study.

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Idiotype vaccines for follicular B cell lymphoma are currently in phase III trials. However, the optimal vaccine formulation is still unknown. Novel strategies will continue to be explored in order to improve upon current protein vaccines. Areas in which improvements would be welcome include increasing the speed of vaccine production and maximizing immunogenicity. Towards this end, we have explored the use of idiotype vaccines produced in plants. This is the first report of the testing of a recombinant virus expressed, plant derived, autologous vaccine in humans. In this trial, single-chain Fv (scFv) idiotype protein vaccine was produced in the plant *Nicotiana benthamiana*, utilizing recombinant technology. The purpose of this phase I study was to explore the feasibility of scFv vaccine production, safety of vaccination, and measurement of immune responses in patients with follicular lymphoma who were in first chemotherapy induced remission. 16 patients were assigned to one of four treatment groups:

Table 1

	scFv Vaccine	scFv Vaccine + GM-CSF
Low Dose (0.2mg)	Group 1 (n=4)	Group 3 (n=4)
High Dose (2.0mg)	Group 2 (n=4)	Group 4 (n=4)

A total of six monthly treatments were planned for each patient. 15 of 16 planned patients have completed vaccination, with one patient showing progression of lymphoma before completion of the vaccine series. There were no significant toxicities or serious adverse events reported during the course of vaccine administration. 10 of 16 patients have developed immune responses to the vaccine. Both humoral and cellular responses were observed. Six patients developed specific cellular immune responses after vaccination: 4/8 in the GM-CSF arms (groups 3,4) versus 2/8 in the non GM-CSF arms (Groups 1,2). One group 4 patient received only 1 of 6 planned rounds of GM-CSF and did not make an immune response. There was no obvious advantage of the high dose (2.0 mg) as compared to the low dose (0.2mg) of vaccine. In conclusion, plant derived scFv idiotype vaccines are feasible to produce, safe to administer and can generate idiotype-specific immune responses. In contrast to previous vaccine formulations, no KLH conjugation was used in this study. A Phase II study utilizing an expanded cohort of patients with follicular lymphoma is planned.

Keywords: Follicular lymphoma\ Idiotype vaccines\ Single-chain Fv